

Remarks

I. Status

Claims 1-74 have been examined. Applicants have amended claims 1-3, 5, 7, 14-16, 29-32, 45-48, and 63-66 in order to more clearly describe Applicants' invention. The claims have been amended to recited that the protein component of the recited oligonucleotide-protein conjugate is formed by a reaction involving a "thiolated" group of the protein, and that this thiolated group is formed by thiolation of an amino group of the protein. Support for these recitations can be found *inter alia*, in Figure 1, and at page 9, lines 16-20; page 12, line 27 – page 13, line 9, and in Example 1 of the specification. Applicants have also amended the claims to clarify their antecedent basis. No new matter has been added by any of the requested amendments, which are all fully supported by the originally filed specification.

II. References Missing From Submitted Information Disclosure Statement

Applicants appreciate the assistance of the Examiner in locating the copies of the non-patent references that were previously submitted to the United States Patent & Trademark Office. Applicants understand that all such references are now joined with the files of the present application, and will be considered when preparing the next Official Action. The Examiner is encouraged to contact the undersigned by telephone in the event that any submitted references are found to be missing from the application files.

III. The Objections Pertaining To The Inclusion Of Hypertext Links In The Specification

The Examiner has objected to the original specification due to its inclusion of hypertext links. Applicants have accordingly amended the specification to delete such links. No new matter has been added by this amendment. In light of Applicants' action, it is respectfully submitted that the objection may be properly withdrawn.

IV. The Rejection Of Claims 1-74 As Anticipated (Pursuant To 35 U.S.C. § 102(B)) Or Obvious In Light Of Reddy *Et Al.* (U.S. Patent No. 5,648,213)

The Examiner has rejected claims 1-74 as anticipated (pursuant to 35 U.S.C. § 102(b)) or obvious in light of Reddy *et al.* (U.S. Patent No. 5,648,213). Reddy *et al.* is stated to describe a method of producing an oligonucleotide-protein conjugate which includes the steps of:

- (A) reacting an oligonucleotide containing an amine group with a heterobifunctional reagent having a first reactive group specific for the amine group of the oligonucleotide, and a second reactive group specific for a thiol group of the protein moiety of the oligonucleotide-protein conjugate, and
- (B) reacting the thiol group of the protein with the thiol-reactive group of the heterobifunctional reagent.

In this regard, the Examiner has drawn Applicants' attention to column 5, lines 51-63, to the reaction scheme of column 19, and to Example 1 of the cited Reddy *et al.* Patent. It is alleged that the method and resulting product taught by the cited Reddy *et al.* Patent anticipate the method of claim 1, and the product-by-process of claim 29. The Examiner has expressed concern that the ligand binding assay of claim 63 is anticipated by claim 22 of the cited Reddy *et al.* Patent. Applicants respectfully traverse and request reconsideration in light of the amended claims.

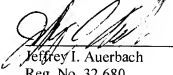
As the Examiner will appreciate, the conjugation method disclosed in Reddy *et al.* involves the conjugation of an activated oligonucleotide to a *cysteine* sulfur of a protein. In this regard, the Examiner will note that the protein component of the conjugate of Example 1 of the cited Reddy *et al.* Patent is merely treated with a reducing agent (i.e., dithioerythritol (DTE), please see, column 18, line 45) in order to prepare it for conjugation with the activated oligonucleotide. In contrast, the present invention comprises an improvement in which conjugation is to be effected using an internal or terminal *amino* group of the protein (please see Figure 1 of the present specification) that has been thiolated (e.g., converted to a thiol group using, for example a reagent such as iminothiolane; please see Example 1 of the present specification). Applicants respectfully submit that such conjugates and methods for preparing and using them are

neither disclosed nor obvious in light of the cited Reddy *et al.* Patent. Applicants further submit that, as indicated in the specification (please see pages 9-10), the method of the present invention provides superior results compared to that of the cited Reddy *et al.* Patent. Accordingly, Applicants respectfully submit that the rejection of claims 1-74 as anticipated (pursuant to 35 U.S.C. § 102(b)) or obvious in light of Reddy *et al.* (U.S. Patent No. 5,648,213) may therefore be properly withdrawn.

Having now fully responded to all of the Examiner's objections and rejections, Applicants respectfully submit that the present application is in condition for Allowance, and earnestly solicit early notice of such favorable action. The Examiner is respectfully requested to contact the undersigned with respect to any issues regarding this application.

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Respectfully Submitted,


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